Safety Data Sheet

Chlorambucil

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS ABSORBED THROUGH THE INTESTINAL TRACT. IT IS TOXIC, CARCINOGENIC, MUTAGENIC, AND TERATOGENIC. IT MAY IRRITATE TISSUES. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND WATER.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, DRINK PLENTY OF MILK OR WATER. INDUCE VOMITING. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. USE ACETONE TO DISSOLVE COMPOUND. WASH DOWN AREA WITH SOAP AND WATER. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

Chlorambucil is an off-white crystalline or powdery solid. It is toxic and carcinogenic to humans (bone marrow and thyroid are chief target organs) and rodents, highly irritating to skin and eyes, and mutagenic and teratogenic in laboratory animals. Its mode of action is that of an alkylating agent. Chlorambucil is used as an antineoplastic agent in the treatment of conditions associated with proliferation of white blood cells and in immunosuppressive therapy.

B. Chemical and Physical Data

1. Chemical Abstract No.: 305-03-3

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Synonyms:

Ambochlorin

Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]- (9CI)

4-[Bis(2-chloroethyl)aminophenyl] butyric acid

gamma-[p-Bis(2-chloroethyl)aminophenyl] butyric acid

4-(p-[Bis(2-chloroethyl)amino]phenyl) butyric acid

4-[p-Bis(beta-chloroethyl)aminophenyl] butyric acid

Chloraminophen, chloraminophene

Chlorobutin, chlorobutine

N,N-di-2-Chloroethyl-gamma-p-aminophenyl butyric acid

p-N,N-di(beta-Chloroethyl)aminophenyl butyric acid

gamma-[p-di(2-Chloroethyl)aminophenyl] butyric acid

Elcoril

Leukeran

Leukersan

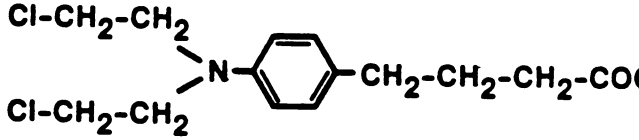
Linfolysin

Phenyl butyric acid nitrogen mustard

Molecular formula: $C_{14}H_{19}Cl_2NO_2$

weight: 304.24

structure:



Density: No data.

Absorption spectroscopy: UV spectra in various solvents are described by Grasselli and Ritchey (1975) and Linford (1962).

Volatility: No data.

Solubility: Soluble in dilute alkali and acids, ether, acetone, and benzene.

8. Description, appearance: Off-white, slightly granular powder or white needles.

9. Boiling point: No data.

   Melting point: 64-66°C.

10. Stability: Sensitive to oxidation and moisture. Light sensitive; stock solutions have limited stability even at freezer temperatures (see D4). The stability of all aqueous systems is poor.

11. Chemical reactivity: As an alkylating agent, chlorambucil reacts with proteins and a variety of nucleophilic compounds by replacement of one or both chlorine atoms. Hydrolyzed in alkaline solution at elevated temperatures.

12. Flash point: No data.

13. Autoignition temperature: No data.

14. Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazard Data

1. Chlorambucil does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.

2. No conditions contributing to instability, other than light sensitivity, are known to exist.

3. No incompatibilities are known.

4. No hazardous decomposition products have been identified.

5. Chlorambucil does not require nonspark equipment. When handled in flammable solvents, the precautions required for such solvents apply.

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving chlorambucil.

1. Chemical inactivation: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by chlorambucil or the materials used for cleanup. If more than

1 g has been spilled or if there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Wash surfaces with copious quantities of water. Glassware should be rinsed (in a hood) with acetone, followed by soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing chlorambucil shall be disposed of in sinks or general refuse. Surplus chlorambucil or chemical waste streams contaminated with chlorambucil shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing chlorambucil shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing chlorambucil shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with chlorambucil shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g. associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing chlorambucil shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid chlorambucil in sealed ampoules or in amber screw-capped bottles or vials with Teflon cap liners. Concentrated stock solutions in ethanol have a shelf life of 6.3 and 31.1 days in refrigerator (4°C) and freezer (-10°C) storage, respectively. Entry of water vapor during storage or sampling of stock solutions must be prevented (Stewart and Owen, 1980).

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: No specific methods have been reported.

2. Separation and analysis: Chlorambucil may be extracted from biological material with benzene or ethyl acetate (Linford, 1962). Colorimetric determination of the blue reaction product of chlorambucil with 4-(p-nitrobenzyl)pyridine has been applied to blood (Boyland et al., 1961) and other biological materials. This method is not specific for chlorambucil but is applicable to many alkylating agents. It may also be adaptable to environmental monitoring. Spectrophotometric determination in blood samples at concentrations of 2 µg/ml or higher has been reported (Linford, 1962). GC-MS, after extraction and formation of the trimethylsylyl derivative, has been used for the determination of chloroambucil in plasma and urine (Chang et al., 1980).

F. Biological Effects (Animal and Human)

1. Absorption: Absorbed from the gastrointestinal tract. While chlorambucil is a severe irritant of skin and eyes, it is not known whether absorption via these routes produces systemic effects.

2. Distribution: Very few data. Radioactivity due to subcutaneously administered ^{3}H-chlorambucil in rats readily appears in the blood-vascular system and, after initial high activity in the liver, is found mainly in the kidney.

3. Metabolism and excretion: After intraperitoneal injection in rats, chlorambucil is first oxidized to the 3,4-dehydro derivative and further by β-oxidation to phenylacetic acid mustard. These oxidation products have been identified in the blood of injected rats. The urine within 24 hours contains none of these products; instead, it contains the major metabolite 2-[4N-(2-chloroethyl)-aminophenyl] acetic acid (loss of one chloroethyl group from phenylacetic acid mustard) (McLean et al., 1980). As may be expected of an alkylating agent, chlorambucil binds covalently to tissue proteins and alkylates DNA (summarized in IARC, 1981).

4. Toxic effects: The acute intraperitoneal LD50s are 14 and 81 mg/kg in the rat and mouse, respectively. In humans, acute toxic effects include lethargy, vomiting, and unconsciousness with grand mal seizures (Wolfson and Olney, 1957). Chronic effects are severe depression of white blood cell count and bone marrow damage in addition to other symptoms usually associated with antineoplastic chemotherapy. Target organs for toxicity are bone marrow and thyroid gland; two cases of irreversible bone marrow failure (Rudd et al., 1975) and thyroid gland atrophy and fibrosis in rats have been reported.

5. Carcinogenic effects: These have been summarized (IARC, 1981). Chlorambucil induces lung, lymphatic, and ovarian tumors in mice and neoplasms in bone marrow and lymphatic organs in male rats (Weisburger et al., 1975). At least 34 cases of cancer have been reported in chlorambucil therapy of nonmalignant diseases, including 31 acute leukemias.

6. Mutagenic and teratogenic effects: Chlorambucil induces mutations in yeast cells and cross-links in the DNA of tumor cells. Teratogenic effects have been reported in chicks, mice, and rats.

G. Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes.

2. Ingestion: Drink plenty of milk or water. Induce vomiting.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician. Observe for delayed vesicant effects. Consider ophthalmological consultation.

References

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